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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,853	ROLLAND ET AL.	
	Examiner	Art Unit	
	DANIEL C. GAMETT	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *04 March 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *03/04/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The preliminary amendments of 03/04/2005 and 01/09/2006 have been entered in full. Claims 1-42 are under examination.

Specification

2. The disclosure is objected to because of the following informalities: The preliminary amendment filed 01/09/2006 indicates an incorrect filing date for priority document 60/4085655.

Appropriate correction is required.

Claim Objections

3. Claim 7 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 7 recites the cell preparation of claim 1, wherein the one or more keratinocytes and fibroblasts naturally secret one or more biologically active molecules. A preparation comprising a cell that secretes a biologically active molecule not recited in claim 1 would infringe claim 7 but not claim 1.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

5. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

6. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

7. Claims 1, 2, 4, 5, and 12-21 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-14 of U.S. Patent No. 7144729. Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

8. Instant claim 1 and allowed claim 1 are each drawn to compositions comprising a first and second component. The respective claims differ as follows: Instant claim 1 recites a first component comprising an extracellular matrix or matrix material containing fibrinogen, wherein the extracellular matrix material is selected from the group consisting of collagens, alginate, alginate beads, agarose, fibrin, fibrin glue, blood plasma, fibrin beads, laminins, proteoglycans, fibronectins, chitosan, and heparin; whereas allowed claim 1 recites only fibrinogen. This difference is obvious in view of allowed claim 4, which recites that the first component further comprises a collagen, alginate, alginate beads, agarose, fibrin, fibrin glue, blood plasma, fibrin

beads, laminin, proteoglycan, fibronectin, chitosan, or heparin. It is further noted that instant claim 11 recites wherein the first component comprises fibrinogen, the identical species in allowed claim 1.

9. Instant claim 1 recites a second component comprising from about $1x10^3$ cells/μl to about 50 $x10^3$ cells/μl..., wherein the cells comprise one or more keratinocytes and fibroblasts. In contrast, allowed claim 1 recites one or more keratinocytes and fibroblasts. This difference is obvious in view of allowed claim 15, which recites that the second component comprising from about $1x10^3$ cells/μl to about 50 $x10^3$ cells/μl.

10. Instant claim 1 recites that the keratinocytes and fibroblasts are allogeneic and mitotically active or inactivated, whereas allowed claim 1 recites only mitotically inactivated allogeneic cells. Thus, the allowed claim recites a species that would anticipate the generic instant claim.

11. Therefore, instant claim 1 and allowed claims 1, 4, 11, and 15 represent different combinations of the same limitations that render the claims mutually obvious. To these base claims, instant claims 12-21 and allowed claims 5-14 respectively add identical limitations.

Claim Rejections - 35 USC § 112

12. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

13. Claims 1-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as

the invention. Claim 1 recites "a second component comprising from about 1 x 10^3 cells/μl to about 50 x 10^3 cells/μl and thrombin to the wound site". It is not clear how "to the wound site" relates to the rest of the description of the component. This appears to be an attempt to incorporate a method step into the claim. A single claim which claims both an apparatus and the method steps of using the apparatus is indefinite under 35 U.S.C. 112, second paragraph. See MPEP 2173.05(p).

14. Claim 1 is further unclear in view of dependent claim 11. Claim 1 recites a first component comprising an extracellular matrix or matrix material containing fibrinogen. Claim 11 recites the cell preparation of claim 1, wherein the first component comprises fibrinogen. Therefore, while fibrinogen does not appear to be optional in claim 1, claim 11 suggests that it is.

15. Claims 13, 26, and 37 recite a cryoprotectant, which may be a 10% or 15% solution of glycerol or a 15% glycerol and 5% human serum albumin solution. It is not clear whether these percentages refer to the final concentrations of glycerol or albumin in the preparations or whether they refer to stock solutions from which an unspecified amount is to be added to the preparation.

16. The term "high barrier performance" in claim 21 is a relative term which renders the claim indefinite. The term "high" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

17. The remaining claims are indefinite as they depend from an indefinite base claim.

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claim 8-10 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The first paragraph of 35 U.S.C. 112 states, "The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same...". The courts have interpreted this to mean that the specification must enable one skilled in the art to make and use the invention without undue experimentation. The courts have further interpreted undue experimentation as requiring "ingenuity beyond that to be expected of one of ordinary skill in the art" (Fields v. Conover, 170 USPQ 276 (CCPA 1971)) or requiring an extended period of experimentation in the absence of sufficient direction or guidance (In re Colianni, 195 USPQ 150 (CCPA 1977)). Additionally, the courts have determined that "... where a statement is, on its face, contrary to generally accepted scientific principles", a rejection for failure to teach how to make and/or use is proper (In re Marzocchi, 169 USPQ 367 (CCPA 1971). Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Colianni, 195 USPQ 150, 153 (CCPA 1977), have been clarified by the Board of Patent Appeals and Interferences in Ex parte Forman, 230 USPQ 546 (BPAI 1986), and are summarized in In re Wands (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed Cir. 1988). Among the factors are the nature of the invention, the state of the prior art, the predictability or lack

thereof in the art, the amount of direction or guidance present, the presence or absence of working examples, the breadth of the claims, and the quantity of experimentation needed. The instant disclosure fails to meet the enablement requirement for the following reasons:

a. *The nature of the invention:* The claimed invention is a cell preparation for tissue regeneration comprising keratinocytes and fibroblasts wherein the cell types are genetically engineered to secrete an exogenous level of one or more biologically active molecules selected from a Markush group of several growth factors and cytokines.

b. *The state of the prior art and the predictability or lack thereof in the art:* The prior art teaches that some of the recited growth factors may generally promote wound healing and tissue regeneration, but they vary in their activity and effectiveness. For example, US 6054122 (25 April 2000; of record) discloses that PDGF, IGF-1, EGF, TGF-α, TGF-β, and FGF applied individually to standardized skin wounds in a porcine model had little effect on the regeneration of connective tissue or epithelium (Col. 3 lines 20-57). In contrast, the combination of PDGF-bb homodimer and IGF-1 or TGF-α yielded excellent connective tissue and epidermal regeneration (Col. 3 lines 20-57). The effects of supraphysiological concentrations, such as would be achieved by the claimed method, are not predictable. Some of the recited cytokines, IL-1β, IL-6, IL-8, and TNFα, are proinflammatory, and so the person of skill in the art would expect to encounter a fine balance between beneficial and detrimental effects for these cytokines. Timing of expression would also be critical because, although inflammation is a normal first step of wound healing, prolonged inflammation would interfere with the subsequent steps of

tissue formation and tissue remodeling (Singer, A. and Clark, R. (1999) "Cutaneous Wound Healing" The New England Journal of Medicine 341:738:746; of record).

c. *The amount of direction or guidance present and the presence or absence of working examples:* Enablement must be provided by the specification unless it is well known in the art. *In re Buchner* 18 USPQ 2d 1331 (Fed. Cir. 1991). The specification does not provide an example of genetically engineered cells in any model of tissue regeneration. The specification does not provide an example of any manipulation aimed at switching any gene on or off, or controlling whether gene expression is constitutive. The specification merely suggests that these procedures might be useful and invites the skilled artisan to determine which gene to switch on or off, how to do it, and for what purpose.

d. *The breadth of the claims and the quantity of experimentation needed:* While the list of factors to be tested is finite, it is large. To practice the invention, the skilled artisan would need to first create the engineered cells and achieve the desired control of gene expression and then test several variables such as the effects of overexpression of each factor alone vs. in combination with other factors, early vs. late in the healing process, in either keratinocytes or fibroblasts alone or in both.

20. The courts have stated that patent protection is granted in return for an enabling disclosure, not for vague intimations of general ideas that may or may not be patentable. Tossing out the mere germ of an idea does not constitute an enabling disclosure. Reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. See *Genentech v. Novo Nordick A/S* (CAFC) 42 USPQ2d 1001 (1997).

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

22. Claims 1, 2, 4, 7, 11, 15, 22, 24, 28-30, 31, 33, 39, and 42 are rejected under 35 U.S.C. 102(e) as being by US Patent 6479052, filed December 2, 1999. Claims 1, 15, 22, and 31 are drawn to a cell preparation comprising fibrinogen, thrombin, and one or more keratinocytes and fibroblasts and to methods of using said preparation. Claims 4, 24, and 36 specify that the cell preparation is in the form of a spray. The '052 patent teaches a method of adhering cells to a tissue by means of spraying a two-component mixture wherein the mixed components form a fibrin polymer (see claim 1). The '052 patent teaches sequential administration of a fibrin component, followed by cells (as in instant claims 33 and 40; see claim 5 in the '052 patent), concurrent spraying of cells and the fibrin-producing components (see claim 6), mixture of component both before and after they reach the wound site (see claims 1 and 11). These teachings anticipate the fibrinogen-thrombin and mode of administration limitations of the instant claims. The '052 patent teaches the use of keratinocytes and fibroblasts (column 2, lines 8-18) in amounts which, after conversion of units, fall with the instantly claimed range (column 13, lines 21-22). . In the absence of evidence to the contrary, it may be assumed that the keratinocytes and fibroblasts recited in the '052 patent include differentiated cells (as in instant

claim 2) that inherently are capable of secreting the biologically active molecules recited in instant claims 1 and 7.

Conclusion

23. No. claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel C. Gamett, PhD., whose telephone number is (571)272-1853. The examiner can normally be reached on 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571 272 0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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DCG
Art Unit 1647
8 January 2008

/David S Romeo/
Primary Examiner, Art Unit 1647